

R E V I E W
A R T I C L E

Prenatal Sonographic Features of Beckwith-Wiedemann Syndrome

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Beckwith-Wiedemann syndrome (BWS) is a congenital overgrowth syndrome, characterized by macrosomia, macroglossia, organomegaly, abdominal wall defects, hemihypertrophy, ear creases/pits, neonatal hypoglycemia, adrenocortical cytomegaly, abdominal wall defects, and an increased frequency of embryonal tumors. It is known to be the result of genetic and epigenetic alterations on chromosome 11p15.5. Most of the affected cases are diagnosed after birth and it is difficult to diagnose prenatally. Currently, ultrasound is viewed as a useful tool in the prenatal detection of affected cases. This article provides an overview of the prenatal sonographic features of BWS, including polyhydramnios, macrosomia, macroglossia, omphalocele, an enlarged placenta, urinary anomalies, gastrointestinal anomalies, fetal hydrops and other rare anomalies. Several diseases may have phenotypic overlaps with BWS including Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome, diabetes in pregnancy complicated with macrosomia, and infantile polycystic kidney disease. Increasing awareness and knowledge of various fetal malformations of BWS on prenatal ultrasound will be helpful in the early detection throughout the gestation. Prenatal diagnosis of fetuses with BWS could help obstetricians and pediatricians in the decision-making process for prenatal, perinatal and postnatal care.

KEY WORDS — Beckwith-Wiedemann syndrome, prenatal ultrasound

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Introduction

Beckwith-Wiedemann syndrome (BWS, MIM 130650), reported by Beckwith [1] in 1963 and Wiedemann [2] in 1964 respectively, is known as an

autosomal inheritance with variable expressions [3]. It is the most common congenital overgrowth condition with typical features in neonates, including macrosomia, macroglossia, organomegaly, abdominal wall defects, hemihypertrophy, ear creases/pits,



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neonatal hypoglycemia, adrenocortical cytomegaly, and an increased risk of pediatric neoplasia. Clinical diagnosis of BWS in the neonatal period was based on the presence of either three major features (omphalocele, macroglossia, gigantism), or two major features plus three minor features (nephromegaly, ear creases/pits, facial nevus flammeus, hypoglycemia, congenital cardiac defects, or hemihypertrophy) [4]. Mental retardation seems to be associated with untreated and profound neonatal hypoglycemia [4]. The incidence of BWS is reported to be approximately 1 in 13,500 live births [5]. The overall risk for development of embryonal malignancies such as Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma and adrenal carcinoma in BWS children is 5–10% [6,7]. The syndrome is known to come from a range of genetic and epigenetic alterations on chromosome 11p15.5 and these alterations can be easily analyzed by molecular tests in the modern era.

Most BWS cases are sporadic and cytogenetically normal. Currently, they are diagnosed postnatally on the basis of physical features and there is still a lack of fixed criteria for early detection of affected fetuses without a positive family history. At present, ultrasound is thought to be a valuable tool in the prenatal detection of characteristic findings associated with BWS. Here, we review the associated sonographic features in fetuses with BWS and the reported prenatal sonographic findings include polyhydramnios, macrosomia, macroglossia, omphalocele, an enlarged placenta, urinary anomalies, gastrointestinal anomalies, fetal hydrops and other rare anomalies. Early diagnosis of fetuses with BWS is significantly beneficial for prenatal counseling, perinatal management such as the mode and time of delivery planning, and postnatal care for neonatal hypoglycemia, respiratory distress and the risk of malignancy. In addition, differential diagnosis including Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome, diabetes in pregnancy complicated by macrosomia, and infantile polycystic kidney disease is discussed here.

Prenatal Sonographic Features

The first prenatal diagnosis of BWS was in 1980 [8]. The prenatal sonographic features of published BWS cases are summarized in Table 1 [8–40].

Increased Amniotic Fluid Amount

The most consistent ultrasound finding in the reported cases was polyhydramnios (Table 1). It can be evident from the second trimester. The cause for the development of polyhydramnios in association with BWS is unclear at present.

Fetal Overgrowth (Macrosomia)

More than one half of BWS cases were prenatally detected with macrosomia (Table 1). Although 87% of individuals with BWS have pre- or postnatal overgrowth, it is unknown about the timing of the onset of overgrowth [4]. Evaluation of the head circumference, abdominal circumference, and estimated fetal weight percentiles of six BWS fetuses demonstrated that affected fetuses may exhibit accelerated growth as early as 25–30 weeks' gestation, but may exceed the 90th percentile only after 36 weeks' gestation [25]. Prenatal detection of polyhydramnios and overgrowth beginning between 25–36 weeks' gestation, even without omphalocele, should alert the clinical physicians to the possibility of BWS [25,30].

Facial Anomaly

The reported facial anomaly associated with BWS is macroglossia. Neonatal macroglossia may result in airway obstruction, which requires surgical resection. Macroglossia is shown to be the most common clinical feature in the BWS patients with the incidence of approximately 82–98% [7,41]. Based on Table 1, the detection rate in the prenatal period is less than in the postnatal period because either

Table 1. Literature review of reported prenatal sonographic features with BWS (A)

[illegible]

Table 1. Literature review of reported prenatal sonographic features with BWS (B)

		Poly-hydramnios	Macro-somia	Macro-glossia	Ompha-locele	Enlarged placentas		Nephro-megaly	Urinary anomalies				Gastrointestinal anomalies				Fetal hydrops	Others
						PMD	Placento-megaly		Renal cysts	Pyelec-tasis	Adrenal tumor	Adreno-megaly	Hepato-megaly	Enlarged pancreas	Pancreatic cyst	Pancreato-blastoma		
	Ranzini et al. Ranzini et al. Ranzini et al.	(+) (+) (+)	(+)		(+)			(+) (+) (+)	(+)				(+)					
1997	Fremont et al.		(+)					(+)										Family history
2000	Fert-Ferrer et al. Fert-Ferrer et al.	(+) (+)	(+) (+)	(+) (+)				(+) (+)							(+)		(+) (+)	
2001	Hamada et al.	(+)	(+)	(+)	(+)			(+)					(+)					Single umbilical artery
2001	Benzacken et al.		(+)					(+)										
2002	Reish et al. Reish et al. Reish et al.	(+) (+) (+)	(+) (+) (+)	(+) (+) (+)			(+) (+) (+)											
2002	O'Connor and Levine				(+)													
2002	Weinstein and Goldstein			(+)	(+)			(+)										
2003	Pelizzo et al.	(+)														(+)		
2004	Le Caignec et al.		(+)					(+)					(+)					
2004	Mulik V et al.					(+)												
2005	Williams et al. Williams et al.	(+) (+)		(+) (+)	(+) (+)			(+) (+)			(+)							
2005	Izbizky et al.	(+)	(+)				(+)											
2007	Grati et al. Grati et al.				(+) (+)													
2007	Aagaard-Tillery et al.																	Single umbilical artery Prominent maternal ovaries

PMD = *placental mesenchymal dysplasia*.

macroglossia may not develop until late fetal life or even after birth [42] or information about the face was neglected on prenatal ultrasound [12].

Abdominal Wall Defect

Omphalocele can be a characteristic prenatal sonographic feature of BWS. Several fetuses with BWS were reported to have had omphalocele (Table 1). Omphalocele complicates about one half of cases in BWS, but less than 3% of all cases with omphalocele are diagnosed as BWS [43]. Two fetuses with BWS with isolated omphaloceles were detected as having a paternal segmental uniparental disomy 11 (UPD11) by molecular analysis of amniotic fluid cells, and the authors supposed that the abdominal organs had a predominant uniparental constitution [39].

Enlarged Placentas

The placental anomalies associated with fetuses with BWS include placentomegaly and placental mesenchymal dysplasia (massive hydrops of placental stem villi). Placental mesenchymal dysplasia, manifested by an enlarged hydropic placenta with numerous cyst-like villi and a lack of trophoblastic hyperplasia, can be a characteristic prenatal sonographic feature of BWS [44–50]. Placental mesenchymal dysplasia is associated with normal fetuses, intrauterine growth restriction, and fetal demise but can also be associated with BWS [50–52]. Cohen et al reviewed 66 reported cases with placental mesenchymal dysplasia and found that 15 cases (23%) were associated with BWS [51]. They supposed that placental mesenchymal dysplasia was associated with a normal or slightly increased level of maternal serum β -human chorionic gonadotrophin (β -HCG), an elevated level of maternal serum α -fetoprotein (AFP), and the presence of a diploid fetus [51]. McCowan and Becroft reported that pregnancies with BWS fetuses, characterized by placentomegaly and placental mesenchymal dysplasia, may present maternal hypertension and proteinuria [45].

Urinary Anomalies

The reported urinary anomalies in association with BWS include nephromegaly, pyelectasis, and adrenal cysts. Several fetuses with BWS were reported to have had hepatomegaly (Table 1). A right hemorrhagic adrenal cyst was reported in a fetus with incomplete BWS at 21 gestational weeks [53]. Bilateral hemorrhagic adrenal cysts were reported in a BWS fetus at 33 gestational weeks [54]. Multicystic kidneys together with polyhydramnios, macrosomia, and placentomegaly were reported in a fetus with incomplete BWS at 26 gestational weeks and the urinary anomalies were confirmed as bilateral adrenal carcinomas [37].

Gastrointestinal Anomalies

The gastrointestinal anomalies associated with BWS include hepatomegaly, a pancreatic cyst, and pancreatoblastoma. Several fetuses with BWS were reported to have the finding of hepatomegaly (Table 1). Anomalies in the pancreas are reported less in the literature. Steigman et al [55] were the first to report a case of true pancreatic cystic dysplasia in BWS. One fetus with a congenital pancreatic cyst and omphalocele at 24 gestational weeks was associated with BWS [26]. Congenital pancreatoblastoma has been reported in BWS neonates [56] and only one BWS fetus was detected with pancreatoblastoma on prenatal ultrasound at 20 gestational weeks [33].

Fetal Hydrops

Fetal hydrops associated with BWS is relatively uncommon. Nonimmune fetal hydrops together with placentomegaly were reported in familial BWS with trisomy 11p15 [23]. Hydrops was detected in a BWS fetus with the cytogenetic result of a distal monosomy 8pter and a distal trisomy 11pter inherited from a paternal balance translocation t(8;11)(p23.2;p15.5) [27].

Rare Anomalies

A single umbilical artery was first reported in a fetus with BWS having the features of macrosomia, macroglossia and omphalocele [28]. They supposed that a single umbilical artery may be related to the omphalocele and not necessarily to the BWS [28]. Another BWS fetus detected with a single umbilical artery was found to have an abnormal maternal serum screen result and prominent maternal ovaries [40]. One fetus with BWS was found to have cardiomegaly, hydronephrosis, hepatomegaly, and macroglossia [22].

Differential Diagnosis

The definite diagnosis of BWS depends on molecular genetic analysis. Owing to the common anomalies in BWS, differential diagnoses should include Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome, diabetes in pregnancy complicated with macrosomia, and infantile polycystic kidney disease.

Sotos Syndrome and Weaver Syndrome

Sotos syndrome is caused by mutation in the *NSD1* gene on 5q35, characterized by rapid overgrowth, acromegalic features, mental retardation, and advanced bone age [57]. Weaver syndrome is also caused by mutation in the *NSD1* gene on 5q35, characterized by accelerated growth and osseous maturation, uncommon craniofacial appearances, hoarse and low-pitched cry, hypertonia and campodactyly [58]. The overgrowth in both syndromes mimics BWS. However, the common features of macroglossia, omphalocele and organomegaly in BWS are not the characteristics in both syndromes.

Simpson-Golabi-Behmel Syndrome

Simpson-Golabi-Behmel syndrome (SGBS), characterized by pre- and postnatal overgrowth, coarse

facies, cardiac diseases, and other congenital abnormalities, is caused by mutations in glypican-3 (*GPC3*) gene on Xq26 [59]. Many clinical features of BWS and SGBS are similar including macrosomia, macroglossia, organomegaly, neonatal hypoglycemia, and a risk of embryonal tumors. However, the major difference is an X-linked recessive pattern in SGBS and an autosomal dominant pattern in BWS.

Diabetes in Pregnancy Complicated with Macrosomia

Diabetes mellitus in pregnancy may result in fetal anomalies such as macrosomia, polyhydramnios and other structural defects. However the difference between this disorder and BWS easily relies on maternal blood glucose levels.

Infantile Polycystic Kidney Disease

Enlarged fetal kidneys are characteristic of more than one possible diagnosis. The prenatal sonographic features of bilateral multicystic mass around kidneys resembling enlarged kidneys and infantile polycystic kidney disease are similar [37]. However infantile polycystic kidney disease is a known entity and is often associated with oligohydramnios. BWS should be considered especially if a normal or increased amount of amniotic fluid and a full bladder are present [11].

Conclusion

Many cases of BWS are detected after birth owing to the difficulty in making a prenatal diagnosis. This article provides an overview of prenatal sonographic features of BWS. Prenatal detection of polyhydramnios, macrosomia, macroglossia, omphalocele, an enlarged placenta, together with urinary anomalies, gastrointestinal anomalies, fetal hydrops and other rare anomalies should alert clinicians to the possibility of BWS and prompt molecular and cytogenetic

Table 2. Prenatal sonographic features of BWS and differential diagnosis

Prenatal sonographic features

Increased amniotic fluid amount (polyhydramnios)
 Fetal overgrowth (macrosomia)
 Facial anomaly
 Macroglossia
 Abdominal wall defect
 Omphalocele
 Enlarged placentas
 Placentomegaly, placental mesenchymal dysplasia
 Urinary anomalies
 Nephromegaly, pyelectasis, adrenal cyst
 Gastrointestinal anomalies
 Hepatomegaly, an enlarged pancreas,
 pancreatoblastoma, pancreatic cyst
 Fetal hydrops
 Rare anomalies
 Single umbilical artery, cardiomegaly

Differential diagnosis

Sotos syndrome
 Weaver syndrome
 Simpson-Golabi-Behmel syndrome
 Diabetes in pregnancy complicated with macrosomia
 Infantile polycystic kidney disease

analyses and counseling for BWS (Table 2). Differential diagnosis should include Sotos syndrome, Weaver syndrome, Simpson-Golabi-Behmel syndrome, diabetes in pregnancy complicated with macrosomia, and infantile polycystic kidney disease (Table 2). Early diagnosis of BWS is helpful for prenatal counseling, perinatal management and postnatal care.

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